Value of ^{18}F-FDG PET/CT Combined With Tumor Markers in the Evaluation of Ascites

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OBJECTIVE. The purpose of this study is to investigate the value of ^{18}F-FDG PET/CT combined with assessment of tumor markers in serum or ascites for the diagnosing and determining the prognosis of benign and malignant ascites.

MATERIALS AND METHODS. Patients with ascites of unknown cause who underwent evaluation with FDG PET/CT were included in this retrospective study. The maximum standardized uptake value (SUV_{max}) and levels of the tumor markers carbohydrate antigen–125 (CA-125) and carcinoembryonic antigen (CEA) in serum and ascites were recorded. The diagnostic values of FDG PET/CT, CEA and CA-125 levels in serum or ascites, and the combination of imaging plus tumor marker assessment were evaluated. Factors that were predictive of survival were also analyzed.

RESULTS. A total of 177 patients were included. Malignant ascites was eventually diagnosed in 104 patients, and benign ascites was diagnosed in the remaining 73 patients. With the use of FDG PET/CT, 44 patients (42.3%) were found to have primary tumors. The sensitivity, specificity, and accuracy of FDG PET/CT were 92.3%, 83.6%, and 88.7%, respectively. CA-125 levels in serum and ascites showed much better sensitivity than did CEA levels, but they showed significantly lower specificity. If the combination of tumor markers and FDG PET/CT was analyzed, the sensitivity, specificity, and accuracy of tumor markers in serum were 96.6%, 78.1%, and 88.7%, and those of tumor markers in ascites were 97.7%, 80.0%, and 90.4%, respectively. Sex may be an important factor affecting survival time (hazard ratio, 0.471; $p = 0.004$), but age, CEA level, and FDG PET/CT findings could not predict survival.

CONCLUSION. FDG PET/CT combined with assessment of tumor markers, especially CEA, increased the efficacy of diagnosis of ascites of unknown causes. Male sex conferred a poorer prognosis, whereas age, CEA level, and FDG uptake had no predictive significance in patients with malignant ascites.

Keywords: ascites, diagnosis, PET/CT, prognosis, tumor marker

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Ascites is an abnormal accumulation of fluid in the peritoneal cavity [1]. Not only is ascites commonly associated with benign diseases, such as chronic hepatic diseases, cardiac insufficiency, tuberculous peritonitis (TBP), and renal diseases, but it is also associated with malignant neoplasms [2–7]. Determining the cause of ascites is challenging. According to previous reports, approximately 75% of ascites developed secondary to hepatic cirrhosis, 10–12% were caused by carcinoma, and 8–10% were caused by peritoneal tuberculosis, renal disease, or pancreatic disease [4, 5].

Biochemical examination and cytologic analysis have been used to determine the causes of ascites. Cytologic analysis is the reference standard for distinguishing between benign and malignant ascites. Its specificity is 100%, but its sensitivity is only approximately 30% [8]. Tumor markers are also widely used in the clinical diagnosis of blood, tissue, and fluid. However, no special tumor marker has both high sensitivity and specificity for malignancy. Imaging modalities, such as CT, sonography, and MRI, are the mainstay for evaluating ascites and peritoneal disease, but some small neoplastic implants are difficult to detect [9–13]. Although laparoscopy has a higher diagnostic accuracy (82.2–96.6%) [14], it is invasive and subject to sampling error.

PET/CT is a noninvasive diagnostic technique based on distinguishing the metabolic differences between benign and malignant tissues, and it is supposed to be performed for patients with high tumor marker levels and negative or uncertain findings from conventional imaging [15]. PET/CT performed with

^{18}F-FDG has been shown to have important clinical value in distinguishing between benign and malignant lesions, identifying the primary tumor, staging tumors, and monitoring for recurrence and metastasis [16, 17].

Previous studies reported different sensitivity and specificity values for FDG PET/CT performed for ascites characterization, ranging from 66.7% to 86.4% [18, 19]. A previous study [20] also showed that levels of tumor markers such as carbohydrate antigen–125 (CA-125) and carcinoembryonic antigen (CEA) in ascites and serum are useful tools in the differential diagnosis of benign and malignant effusions, although the sensitivity and specificity of these markers are not high. The aim of the present study is to retrospectively review and assess the value of FDG PET/CT used alone and in combination with tumor markers in serum or ascites for the differential diagnosis of ascites of unknown cause and to determine prognostic factors for these patients.

TABLE 1: Characteristics of Patients With Ascites

Characteristic	No. (%) of Patients
Age (y)	
< 60	104 (58.8)
≥ 60	73 (41.2)
Range	20–80
Sex	
Male	64 (36.0)
Female	113 (64.0)
Reference standard	
Pathologic analysis	54 (30.5)
Cytologic analysis	49 (27.7)
Long-term clinical follow-up	74 (41.8)
Cause of malignant cases (*n* = 104)	
Unexplained malignancy[a]	33 (31.8)
Ovarian cancer	30 (28.8)
Peritoneal cancer	10 (9.6)
Gastric carcinoma	7 (6.7)
Lymphoma	6 (5.8)
Colon carcinoma	5 (4.8)
Pseudomyxoma peritonei	3 (2.9)
Pancreatic cancer	3 (2.9)
Malignant mesothelioma	2 (1.9)
Cervix cancer	2 (1.9)
Liver and gallbladder malignant tumor	2 (1.9)
Bladder carcinoma	1 (1.0)
Cause of benign cases (*n* = 73)	
Tuberculosis peritonitis	32 (43.8)
Liver diseases	17 (23.3)
Unknown cause[b]	10 (13.7)
Autoimmune disease	5 (6.9)
Nephrotic syndrome	3 (4.1)
Chylous ascites	2 (2.7)
Innocent tumor	2 (2.7)
Primary peritonitis	1 (1.4)
Eosinophils enteritis	1 (1.4)

[a]Patients with unexplained malignant ascites who died without identification of the primary lesions.
[b]Patients with benign ascites of an unknown cause for whom treatment resulted in a cure.

Materials and Methods

Patients

We retrospectively reviewed patients with ascites who underwent FDG PET/CT in our PET Center from January 2010 to December 2014.

The patients included in the present study were divided into two categories. The 16 patients included in the first category had negative findings of preliminary examinations such as CT, ultrasound, blood tests, or cytologic analysis. The primary cause of the ascites was undetermined, and whether the ascites was malignant or benign was uncertain. The patients in the second category had positive findings of preliminary examinations, but it could not be confirmed whether the findings were the primary cause of the ascites or whether the ascites was malignant or benign. A total of 161 patients were included in this second category, including 35 patients with cytologic findings positive for malignancy, 144 with positive tumor marker levels (in blood, ascites, or both), and 37 with positive findings from other imaging methods or endoscopy.

Patients who had a blood glucose level of more than 12 mmol/L (216 mg/dL) were excluded from this study. Tumor markers (CEA and CA-125) in serum or ascites were also recorded if they had been evaluated.

The final results were confirmed using the reference standard, which was pathologic diagnosis, cytologic examination of ascites, or clinical follow-up. True-positive and true-negative findings indicated that the results of FDG PET/CT were consistent with results obtained using the reference standard. False-positive cases were defined as cases that had no evidence of malignancy detected by the reference standard but had FDG PET/CT results that suggested malignancy. In contrast, false-negative cases were defined as cases that had no evidence of malignancy evident on FDG PET/CT images but had subsequent proof of malignancy identified using the reference standard. The mean follow-up duration was 16 months (range, 5–36 months). The time of death was the endpoint of follow-up.

FDG PET/CT Protocol

Compound FDG was synthesized automatically after ^{18}F was produced by a cyclotron (MINI trace, GE Healthcare), with a radiochemical purity greater than 95%. All patients fasted for at least 6 hours before the administration of FDG. FDG (3.7–4.4 MBq/kg) was injected IV. Approximately 60 minutes after injection of FDG, patients reclined in a quiet room with minimal activity before undergoing FDG PET/CT image acquisition. Imaging was performed using a Discovery VCT FDG PET/CT system (GE Healthcare). A low-dose CT scan was obtained for attenuation correction, with use of the following parameters: tube voltage of 120 kV, tube current of 80 mA, and section collimation of 3.75 mm. A PET scan was then immediately acquired from the level of the head to the upper part of the legs in 2D mode at 3 minutes per bed position. PET data were reconstructed with the ordered set expectation maximization algorithm, and attenuation was corrected by CT images. Data from both CT and PET were sent to a nuclear medicine workstation (Xeleris Workstation, GE Healthcare) for clinical evaluation. The standardized uptake value (SUV) of the lesions was calculated as tissue activity (expressed as megabecquerels per milliliter of tissue) divided by injected dose (expressed as megabecquerels per gram of body weight).

Image Interpretation

Two experienced nuclear medicine physicians independently reviewed all FDG PET/CT images and provided diagnoses separately. Discrepancies were resolved through discussion or via consultation with other nuclear medicine physicians re-

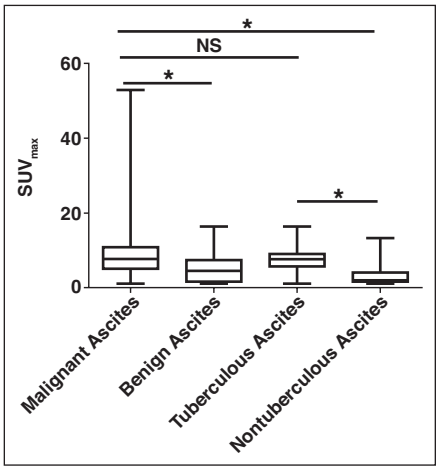

Fig. 1—Box-and-whisker plot of comparison of maximum standardized uptake value (SUV_{max}) in malignant, benign, tuberculous, and nontuberculous ascites. Horizontal lines within boxes denote mean values, and vertical lines and whiskers denote SD. Asterisk denotes significant difference ($p < 0.001$). NS = no significance.

garding the final diagnosis based on FDG PET/CT images. All nuclear medicine physicians were blinded to the reference standard outcome.

Positive FDG PET/CT findings included evidence of primary malignant lesions or increased uptake of FDG on the peritoneum, with CT images of the corresponding area showing peritoneal thickening of nodules, lumps, or other irregular morphologic changes. If morphologic changes were found on CT images, then we considered the findings to denote malignancy, even if no obvious abnormal FDG uptake was noted in the peritoneum.

Negative FDG PET/CT findings were defined as either no clear evidence of malignant peritoneal lesions or observation of smooth thickening of the peritoneum with or without increased FDG uptake, especially when peritoneal or lymph nodes calcification were found. If these findings were present, then benign ascites was diagnosed.

Using the nuclear medicine workstation, the maximum standardized uptake value (SUV_{max}) was recorded in ROIs drawn over the lesions identified by the nuclear medicine physicians as having the most intense uptake. We selected the highest SUV_{max} identified for each patient. If the conclusion from a patient's FDG PET/CT report was malignancy or suspicion for malignancy, we considered the FDG PET/CT to have positive findings for malignancy.

Tumor Markers in Serum and Ascites

The tests of CA-125 and CEA levels in serum and ascites were processed using a modified and advanced form of the enzyme-linked immunosorbent assay (Chemiluminescence Microparticle Immuno Assay, Fujirebio Diagnostics). Ascites was obtained using paracentesis. Tumor marker levels were measured within 1 week of the FDG PET/CT examination. The normal levels of CA-125 and CEA in serum and ascites were less than 35 U/mL and 5.0 μg/L, respectively.

Statistical Analysis

All quantitative data were expressed as mean (± SD) values. The independent samples *t* test was used for the continuous variables. The sensitivity, specificity, accuracy, negative predictive value (NPV), and positive predictive value (PPV) of the diagnostic approaches were calculated. The chi-square test was used to determine differences in the diagnostic value. Cox proportional hazards regression analysis was used to analyze the prognostic variables. The Kaplan-Meier method was used for the analysis of predictive factors. All statistical analyses were performed using statistical software (SPSS software, version 17.0, SPSS). For all analyses, $p < 0.05$ was considered to denote statistical significance.

Results

Patients

A total of 177 patients (64 men and 113 women) with initially unknown causes of ascites were included in this retrospective study. The mean patient age was 56 ± 13 years (range, 20–80 years). A total of 104 patients had malignant ascites, and 73 patients had benign ascites. The characteristics of the patients are presented in Table 1.

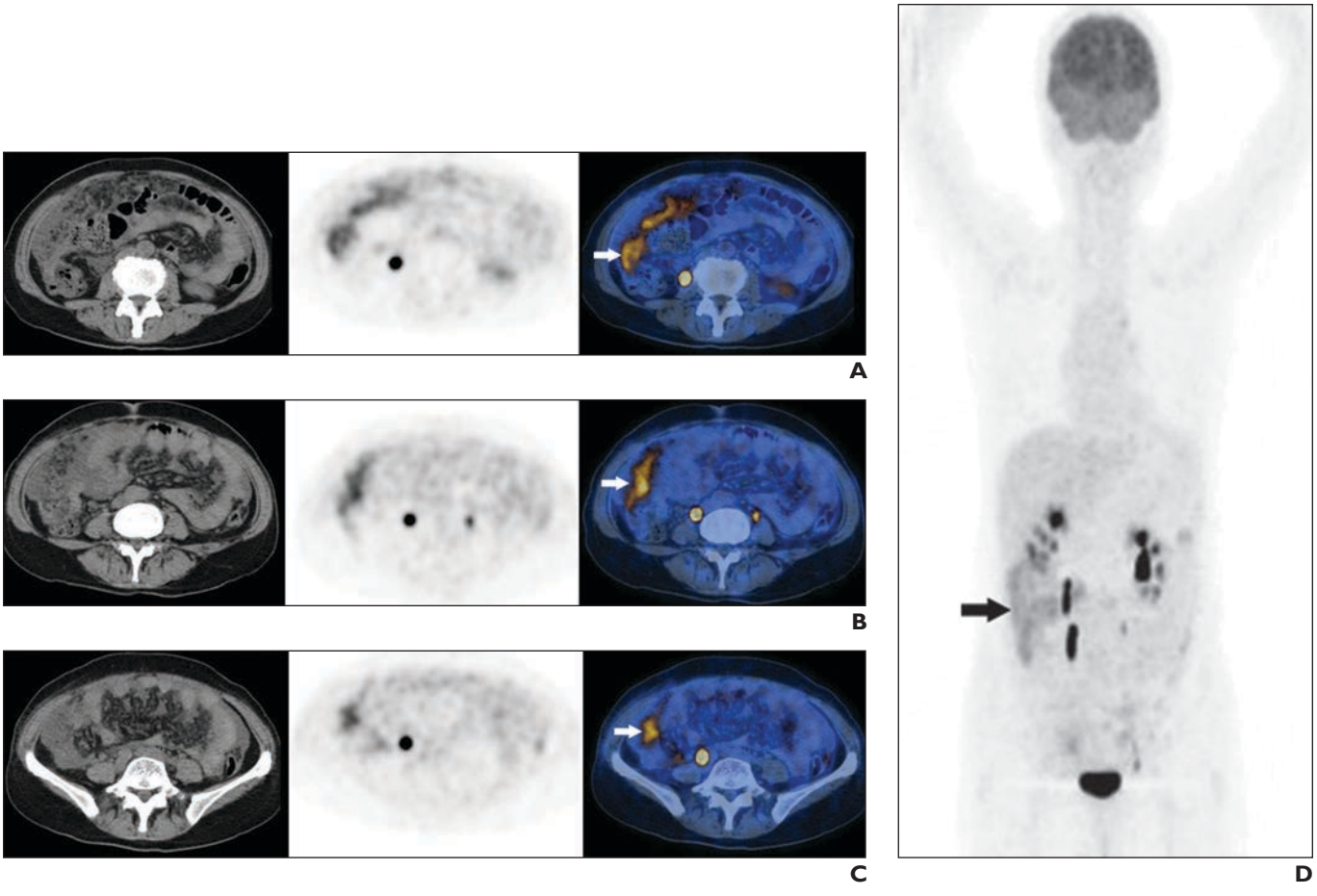

Fig. 2—63-year-old woman with ascites and abdominal pain. Diagnosis based on ^{18}F-FDG PET/CT examination was malignant disease. Pathologic diagnosis was moderately differentiated peritoneal cancer. Patient received chemotherapy for 3 months and died 8 months after undergoing FDG PET/CT examination.
A–**C,** CT (*left column*), PET (*middle column*), and fused (*right column*) images show different parts of abdomen and pelvis, with fused images showing increased uptake on omentum (*arrow*, **A**), peritoneum (*arrow*, **B**), and pelvis (*arrow*, **C**).
D, Maximum-intensity-projection PET image shows foci of increased uptake (*arrow*) on omentum, peritoneum, and pelvis.

Diagnostic Performance of FDG PET/CT

In the present study, FDG PET/CT provided the correct diagnosis for 96 of 104 patients with malignant ascites and 61 of 73 patients with benign ascites. Furthermore, 44 patients (42.3%) had primary tumors detected by FDG PET/CT.

Eighteen misdiagnosed cases were identified on FDG PET/CT images, including eight false-negative cases and 10 false-positive cases. The false-negative cases consisted of two cases of ovarian cancer, one case of uterine cancer, one case of lymphoma, one case of peritoneal cancer, and three cases of ascites of unknown origin. The false-positive cases included four cases of TBP, one case of severe liver cirrhosis, one case of eosinophilic enteritis, one case of sigmoid colon villous adenoma, and three cases of unknown cause.

The overall sensitivity, specificity, accuracy, PPV, and NPV of FDG PET/CT for the diagnosis of ascites were 92.3%, 83.6%, 88.7%, 88.9%, and 88.4%, respectively. Our results showed that the mean SUV_{max} was higher in malignant ascites than in benign ascites (8.6 ± 6.3 vs 5.0 ± 3.7, respectively; $p = 0.000$). On analysis of the mean SUV_{max} in malignant ascites ($n = 104$) and tuberculous ascites ($n = 32$), we found no significant difference between the groups (8.6 ± 6.3 vs 6.3 ± 3.2, respectively; $p = 0.343$). In addition, the mean SUV_{max} in tuberculous ascites and nontuberculous ascites was 7.5 ± 3.2 ($n = 32$) and 3.1 ± 2.8 ($n = 41$), respectively, indicating that the difference between the groups was statistically significant ($p = 0.000$) (Fig. 1).

Features of Malignant Ascites on FDG PET/CT

Peritoneal and omental involvement was observed in 85 patients with malignant ascites (85/104). PET showed that foci of increased uptake were mostly on the peritoneum, especially in the middle upper abdomen and the right paracolic gutter, as shown in Figure 2. Meanwhile, CT showed pronounced thickening, hyperattenuation, or nodularity in the corresponding location.

A total of 30 patients had ovarian cancer diagnosed on the basis of histologic findings or follow-up examination, and the detection rate was 90% (27 of 30 patients) with the use of FDG PET/CT. For those cases, we identified some specific characteristics on the images. First, foci with increased FDG uptake were noted in the omentum, peritoneum (Figs. 3A and 3B), and ovaries (Fig. 3C), with some foci defined as pelvic lymphadenopathy. Second, a wide band of increased uptake of FDG was present on the omentum (Fig. 3D). Third, Douglas pouch involvement (Fig. 3D) was noted in 16 of 30 patients with ovarian cancer.

Of note, a wide band of increased uptake of FDG on the omentum (Fig. 3D) was seen

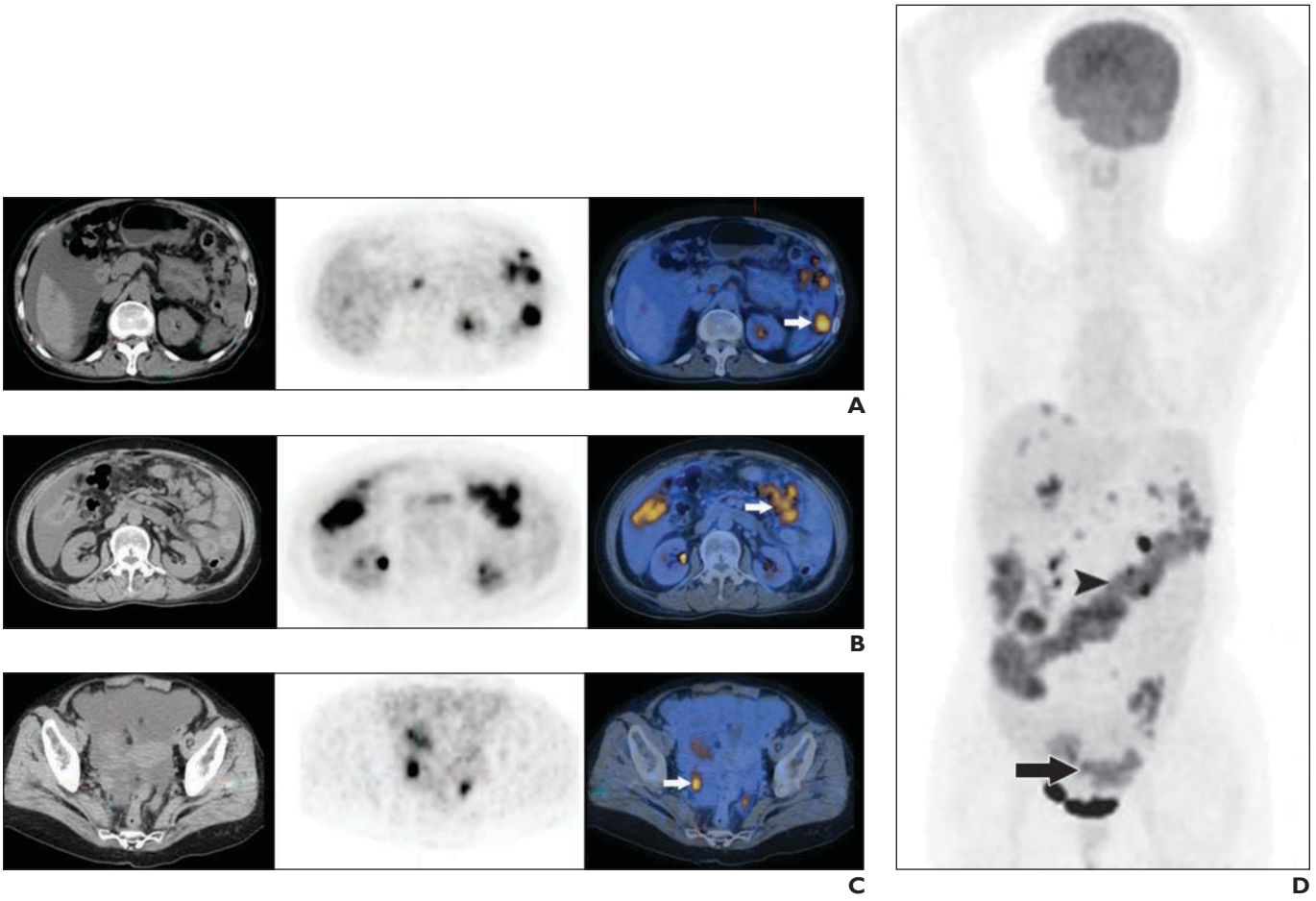

Fig. 3—59-year-old woman with history of abdominal distention for 20 days. Findings from cytologic analysis of ascitic fluid were negative for malignancy. Pathologic diagnosis was ovarian cancer.
A–**C,** Axial CT (*left column*), PET (*middle column*), and fused (*right column*) images reveal foci of increased uptake in omentum, right hemidiaphragm, and nodules in abdominal cavity and pelvis (*arrow*, **A** and **B**) and enlarged right ovary (*arrow*, **C**).
D, Maximum-intensity-projection PET image shows wide band of increased uptake of FDG on omentum (*arrowhead*) and involvement of Douglas pouch (*arrow*).

in 85 of 104 patients with malignant ascites, which suggests that this feature is a relatively specific sign for malignancy.

Features of Benign Ascites on FDG PET/CT

Most benign ascites showed a normal pattern of FDG uptake on FDG PET/CT, but some benign diseases also accumulated FDG and caused false-positive results, especially TBP. TBP is very common in China, accounting for 43.8% of cases of benign ascites (32 of 73 patients) in the present study.

We summarized the FDG PET/CT features of 32 cases of TBP. First, the pattern of FDG uptake was streaklike surrounding the peritoneal surface of the liver and omentum and had a heterogeneous pattern (Fig. 4B–D). Second, most of the omentum was of normal thickness. Third, the foci were often accompanied by lymphadenopathy with high uptake (Figs. 4A and 4D). Calcified and uncalcified nodes in the mediastinum and diaphragmatic and subclavian areas also featured increased metabolism.

Diagnosis Performance of Tumor Markers in Serum and Ascites

Serum levels of CA-125 and CEA were available for 151 of 177 patients, whereas ascites levels of the two tumor markers were available for 73 patients. Table 2 shows the serum and ascites levels of CA-125 and CEA in patients with malignant and benign disease. No significant difference was noted in the levels of CA-125 in serum and ascites between patients with malignant and benign diseases, but the levels of CEA in serum and ascites were significantly different in the two patient groups ($p < 0.05$).

The diagnostic value of serum and ascites levels of CA-125 and CEA is shown in Table 3. On the whole, the accuracy of the CEA level in ascites was much higher than that of the CA-125 level. Both in serum and ascites, the CA-125 level was much more sensitive but less specific than was the CEA level in the characterization of ascites.

Diagnosis Performance of FDG PET/CT Plus Tumor Markers

We also combined FDG PET/CT results with assessment of tumor marker levels in serum or ascites to assess the diagnostic efficacy of this combination. The criterion for the diagnosis of the malignant disease included positive results of at least two evaluations (i.e., FDG PET/CT, CEA level, or CA-125 level). If the combination of tumor markers and FDG PET/CT was analyzed, the sensitivity, specificity, and accuracy of tumor markers in serum were 96.6%, 78.1%, and 88.7%, and those of tumor markers in ascites were 97.7%, 80.0%, and 90.4%, respectively. Table 4 shows our findings, which indicated that FDG PET/CT combined with the ascites level of CA-125 or CEA improved the NPV, compared with FDG PET/CT alone.

TABLE 2: Levels of Tumor Markers Carbohydrate Antigen–125 (CA-125) and Carcinoembryonic Antigen (CEA) in Malignant and Benign Ascites

Ascites Group and Finding	CA-125 Level (U/mL)		CEA Level (μg/mL)	
	In Serum	In Ascites	In Serum	In Ascites
Malignant ascites				
Tumor marker level, mean (± SD)	599.2 ± 490.1	1133.4 ± 501.4	35.3 ± 129.0	327.0 ± 626.8
No. of patients with tumor marker	87	44	87	44
Benign ascites				
Tumor marker level, mean (± SD)	470.0 ± 400.7	898.9 ± 713.9	2.5 ± 3.8	6.7 ± 29.0
No. of patients with tumor marker	64	29	64	29
t Statistic	1.361	1.650	2.372	3.383
p	0.175	0.100	0.020	0.002

Prognostic Factors in Malignant Ascites

Of the 104 patients with malignancy, 61 died, and 43 survived with disease at the end of the follow-up. The median survival for patients with positive and negative FDG PET/CT findings for malignant ascites was 10.6 months and 12.0 months, respectively, which showed no significant difference ($p = 0.549$). Figure 5 shows the survival curve according to the following factors: sex, age, FDG PET/CT findings, and CEA levels in serum and ascites. Of interest, we found that sex seemed to be the only factor that was significantly associated with the prognosis, which was also verified by Cox proportional hazards regression analysis (hazard ratio, 0.471; 95% CI, 0.283–0.785; $p = 0.004$). Analysis indicated that male patients with malignant ascites had a poorer prognosis. In contrast, other factors, including age, FDG PET/CT findings, and CEA level, could not predict survival to a significant degree.

Discussion

Early diagnosis of the cause of ascites is crucial in making a valid treatment plan and predicting prognosis. FDG PET/CT had high diagnostic efficacy for detecting malignant lesions, with a detection rate of 93.3% (97 of 104 cases), and it was helpful in detecting the primary tumor. Our study revealed some other major findings. First, the CEA level in ascites had a very high diagnostic specificity, whereas the CA-125 level in serum or ascites had a high sensitivity but a very low specificity. Evaluation involving the combination of FDG PET/CT with assessment of tumor markers, especially CEA and CA-125 levels in ascites, increased the efficacy of diagnosing ascites of unknown cause. Second, TBP was the main false-positive find-

TABLE 3: Diagnostic Efficacy of Levels of Tumor Markers Carbohydrate Antigen–125 (CA-125) and Carcinoembryonic Antigen (CEA) in Serum and Ascites

Diagnostic Efficacy Value	Serum				Ascites			
	CA-125 Level	CEA Level	χ^2 Value	p^a	CA-125 Level	CEA Level	χ^2 Value	p^b
Sensitivity	98.9	26.4	112.3	< 0.0001	97.8	43.2	71.7	< 0.001
Specificity	3.1	90.6	153.7	< 0.0001	13.8	93.1	126.4	< 0.001
Accuracy	58.3	53.6	0.45	0.503	32.2	63.0	19.0	< 0.001
PPV	58.1	79.3	10.45	0.001	64.3	90.5	19.6	< 0.001
NPV	66.7	47.5	7.52	0.006	80.0	51.9	17.6	< 0.001

Note—Except where otherwise indicated, data are percentage values. PPV = positive predictive value, NPV = negative predictive value.

[a]Difference between levels of CA-125 and CEA in serum.

[b]Difference between levels of CA-125 and CEA in ascites.

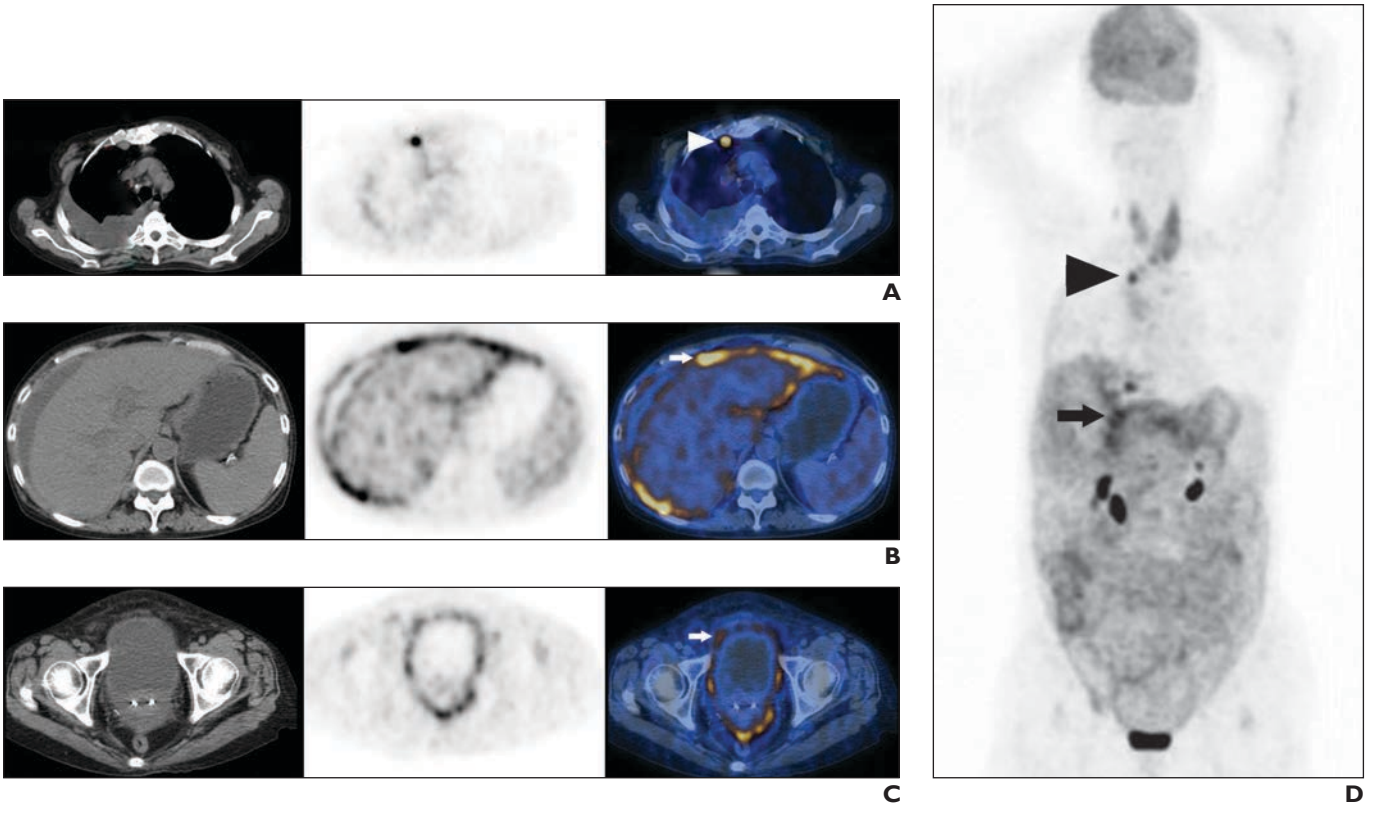

Fig. 4—57-year-old woman with ascites. Findings from cytologic analysis of ascitic fluid were negative for malignancy. Findings from gastroscopy and colonoscopy were also negative for malignancy. Patient received antituberculosis therapy for 1 year; ascites disappeared and cure was achieved.
A–D, Axial CT (*left column*), PET (*middle column*), and axial fused (*right column*) images and maximum-intensity-projection PET image (**D**) show increased uptake of FDG along peritoneal surface of hepatic capsule (*arrow,* **B–D**). Parasternal lymphadenopathy (maximum standardized uptake value, 4) (*arrowhead*, **A** and **D**) was observed.

ing in the present study, which suggests that it should be included in the differential diagnosis in countries where there is a high incidence of tuberculosis. Third, we summarized the FDG PET/CT features of benign and malignant ascites in these 177 patients. Our findings suggested that a wide band of increased uptake of FDG on the omentum was a feature of malignancy, whereas heterogeneous uptake of FDG in a thin layer over the peritoneal surface of the liver and omentum was a feature of benign TBP. Last, sex was the only prognostic factor in this set of patients with malignant ascites. Men with malignant ascites had a shorter survival time than women with malignant ascites. It was surprising that the FDG uptake and the CEA levels in serum and ascites were not predictive factors. To our knowledge, this is the first report assessing the use of the combination of FDG PET/CT and tumor markers in the diagnosis and prognosis of ascites of unknown causes.

In the present study, 96 of 104 patients with malignant ascites and 61 of 73 patients with benign ascites were given a correct diagnosis by FDG PET/CT. A total of 44 patients (42.3%) had primary tumors detected by FDG PET/CT. The most common cause of malignant ascites in our study was ovarian cancer, and the most common cause of benign ascites was TBP. The sensitivity of FDG PET/CT for the detection of primary lesions in patients with ascites was 51.4%. This finding is consistent with those of previously published reports [21–24], which showed that FDG PET could identify the primary tumor in 25.0–63.3% of patients with metastatic carcinoma of unknown primary cause. In the present study, the sensitivity, specificity, and accuracy of FDG PET/CT were 92.3%, 83.6%, and 88.7%, respectively. Zhang et al. [18] found that sensitivity, specificity, and accuracy of FDG PET/CT were 86.4%, 83.3%,

TABLE 4: Diagnostic Efficacy of ^{18}F-FDG PET/CT and Evaluation of Tumor Markers Carbohydrate Antigen–125 (CA-125) and Carcinoembryonic Antigen (CEA) in Serum and Ascites

Diagnostic Efficacy Value	FDG PET/CT	Serum Tumor Markers Plus FDG PET/CT	p^a	Ascites Tumor Markers Plus FDG PET/CT	p^b
Sensitivity	92.3	96.6	0.184	97.7	0.080
Specificity	83.6	78.1	0.323	80.0	0.509
Accuracy	88.7	88.7	1.000	90.4	0.694
PPV	88.9	85.7	0.522	87.5	0.759
NPV	88.4	94.3	0.138	96.0	0.045

Note—Except where otherwise indicated, data are percentage values. PPV = positive predictive value, NPV = negative predictive value.
[a]Difference in diagnostic efficacy of combination of assessment of CA-125 and CEA levels in serum and FDG PET/CT versus diagnostic efficacy of FDG PET/CT only.
[b]Difference in diagnostic efficacy of combination of assessment of CA-125 and CEA levels in ascites and FDG PET/CT versus diagnostic efficacy of FDG PET/CT only.

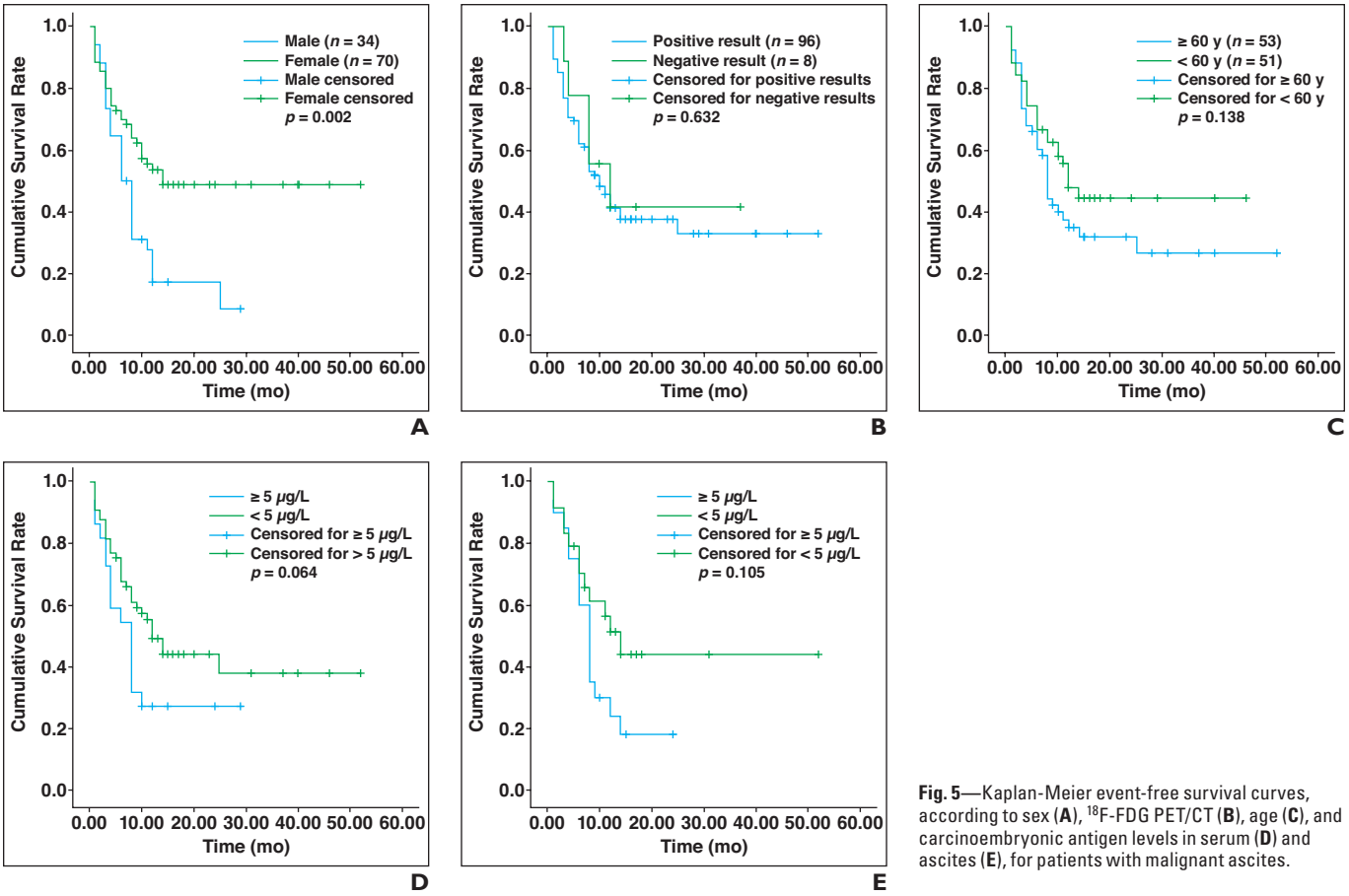

Fig. 5—Kaplan-Meier event-free survival curves, according to sex (**A**), ^{18}F-FDG PET/CT (**B**), age (**C**), and carcinoembryonic antigen levels in serum (**D**) and ascites (**E**), for patients with malignant ascites.

and 85%, respectively. Suzuki et al. [19] and Turlakow et al. [25] reported that the sensitivity of PET plus CT for peritoneal metastasis detection ranged from 66.7% to 78%.

There may be reasons for the higher sensitivity noted in the present study. One reason is the larger sample size (177 patients in the present study vs 35–88 patients in other studies [18, 19, 25]), which decreases the possibility for random error. A second reason was that CT and PET images were acquired during one examination, which obviated software registration and accurately aligned anatomic and functional images in a single scan. A previous study [25] reported that it might affect sensitivity if PET and CT examinations were performed separately with the use of different equipment and with a time lag between the acquisitions. Not only does FDG PET/CT sthe abdominal lesions, but it also provides evidence of disease in other regions of the body. It can help provide a relative comprehensive assessment of a patient's condition. In addition, FDG PET/CT may facilitate the specific identification of biopsy sites to improve the accuracy rate of pathologic diagnosis. Furthermore, PET/CT may also play an important role in the follow-up and evaluation of treatment response, in which case SUV_{max} values could be compared [26, 27]. Song et al. [28] recommended PET/CT as a primary option when the patient presenting with ascites was suspected of having malignancy or TBP.

However, FDG PET/CT still produced false-negative and false-positive results. In the present study, FDG PET/CT found eight false-negative findings and 10 false-positive findings. The main reason for false-negative findings was low uptake of FDG by malignant lesions or the high-uptake background obscuring the lesions [21]. In these cases, low uptake may also relate to the low expression of glucose transporter 1, or a low ratio of hexokinase to glucose-6-phosphate [29–31]. Another reason is the small size of some primary lesions, which may be missed because of partial volume effect, especially when the lesion has low FDG uptake [30, 31]. Primary tumors with growth restricted by the immune system may also have decreased uptake [18].

Increased glucose metabolism in inflammatory tissues, especially Langhans giant cells and lymphocytes in tuberculous nodules, could increase the uptake of FDG [32], which was the main cause of the false-positive FDG PET/CT finding. In the present study, TBP was the main cause, which is consistent with the findings of previous studies [33–36]. Takalkar [37] also suggested that TBP can accumulate FDG with a high SUV_{max} and mimic malignancy. We found that TBP indeed showed a hypermetabolic pattern, and it was really difficult to differentiate malignancy from TBP on the basis of the SUV_{max} only (mean SUV_{max} for malignancy vs TBP, 8.6 ± 6.3 vs 6.3 ± 3.2; $p > 0.05$). However, the characteristics of benign ascites that we summarized in this study may be helpful. On the other hand, some patients with severe cirrhosis or with empyema may have peritoneal thickening and adhesions develop simultaneous spontaneous bacterial peritonitis develops, and the accumulation of FDG would be caused by the large number of inflammatory cells.

For the tumor marker analysis, no significant difference was noted between the serum and ascites levels of CA-125 in malignant and benign ascites ($p = 0.184$ and $p = 0.133$, respec-

tively), which suggests that CA-125 is useless in differentiating malignant from benign ascites, a finding that agrees with findings from a prior study [38]. Of interest, the serum CA-125 level in patients with TBP was usually elevated (n = 26), with a mean value of 529 U/mL. This agrees with the results of a study by Piura et al. [39]. Other reports have stated that the presence of ascites and high CA-125 levels may indicate the presence of malignant lesions in women of childbearing age [36, 38]. It has been pointed out that there are some benign conditions known to cause increases in CA-125 levels, such as gastritis, diverticulitis, cirrhosis, and other cholestatic, pancreatic, and hepatic diseases [40–42], which decrease the specificity of this tumor marker.

Although the CA-125 level in serum and ascites was not very useful diagnostically, the CEA level in both serum and ascites showed the potential ability to differentiate malignant from benign ascites, with a high specificity of 90.6% and 93.1%, respectively, but the sensitivities were quite low. Kaleta et al. [38] showed sensitivity and specificity of 31% and 95%, respectively, when using a CEA level of 3.5 ng/mL was used as a diagnostic cutoff. Caglar et al. [43] found that when the serum CEA cutoff value was of 5.7 ng/L or greater, the sensitivity and specificity were 70.6% and 94.4%, respectively. In other previous reports, the suggested cutoff level of CEA ranged from 3 to 40 ng/mL [44, 45]. The wide range may be caused by the different categories of malignant diseases and the sample sizes.

Because FDG PET/CT produces false-negative or false-positive results, combining FDG PET/CT with tumor markers may be helpful for diagnostic efficacy. However, the sensitivity, specificity, and accuracy did not improve much with the tumor marker values compared with FDG PET/CT alone, except for the NPV obtained with the ascites level of CA-125, ascites level of CEA, and FDG PET/CT. It should be noted that the specificity was not increased. One reason may be related to whether the malignant cells secrete specific tumor markers. For example, the CEA level is always elevated in malignant tumors of the digestive system, such as gastric cancer, pancreatic cancer, and colon cancer, which suggests its application in these tumors. CA-125 has important significance in the diagnosis and follow-up of ovarian cancer. However, the malignant tumors of the digestive system and ovarian cancer represented only 40.3% of all malignant cases involved in this study.

Sex was an important factor for predicting the prognosis of malignant ascites in the present study, whereas age, FDG uptake, and the CEA level in serum or ascites had no predictive significance for the prognosis. Many studies have reported that SUV_{max} has potential prognostic value in many malignant tumors [46–49]. However, it had no predictive value in this group of patients. The reasons may be related to the variety of primary tumors with different biologic behaviors. Furthermore, we noticed that only eight patients had negative PET findings, but 96 had high FDG uptake. Differences in sample sizes for the groups may affect the final results. All patients with ascites had a high CA-125 level in serum and ascites, which makes it impossible to perform the survival and predictive analysis.

The reasons for ascites are very complicated. Nineteen different diseases were identified among the 177 patients in this study, including 33 cases of unexplained malignant ascites and 10 cases of benign ascites of unknown cause. The variety of causes and the unexplained cases may have influenced the results obtained in the present study. Moreover, this study was also limited by its retrospective nature and unavoidable selection bias. In addition, not all patients had available data on tumor markers in serum and ascites. Hence, a prospective paired study with a larger sample is needed to better assess diagnostic efficacy for ascites.

Conclusion

Examination with FDG PET/CT combined with assessment of tumor markers, especially CEA, increased the efficacy of diagnosing ascites of unknown causes. TBP should be included in the differential diagnosis in countries with a high incidence of tuberculosis. Male sex conferred a poorer prognosis, whereas age, CEA, and FDG uptake had no predictive significance for patients with malignant ascites.

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